

PREPARATION OF 5-NITRO-TETRAHYDRO-1,3-OXAZINE-2-ONES*

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Abstract—2-Oxo-derivatives of 3-cyclohexyl-5-alkyl-5-nitrotetrahydro-1,3-oxazine and 3-benzyl-5-alkyl-5-nitro-tetrahydro-1,3-oxazine were prepared. Infrared spectra of compounds obtained were investigated.

IN CONTINUANCE of the investigations on preparation of 5-nitro-tetrahydro-1,3-oxazine derivatives (cf. an extensive review by Eckstein and Urbański,¹) 5-nitro-tetrahydro-1,3-oxazines containing the carbonyl group in position 2 were synthesized.

5-Nitro-tetrahydro-1,3-oxazin-2-ones have not yet been described in the literature. Franchimont and Lublin² reported on 3-nitro-derivative of tetrahydro-1,3-oxazin-2-one which was prepared by the reaction with nitric acid (nitro group attached to the nitrogen atom of the oxazine ring). Tetrahydro-1,3-oxazin-2-ones and tetrahydro-1,3-oxazin-2,4-diones without the nitro group in the ring, are also known.

These compounds have been prepared by using carbonic acid derivatives such as ethyl chloroformate,³ ethylene glycol carbonate,⁴ di(*p*-cresyl)-carbonate,⁵ diethyl carbonate,⁶ chloroformamide,⁷ urea,⁸ thiourea,⁹ isocyanate^{10,11} and cyanamide.¹² For preparation of tetrahydro-1,3-oxazin-2-one, phosgene was also

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¹ Z. Eckstein and T. Urbański, 1,3-Oxazine Derivatives, in *Advances in Heterocyclic Chemistry*, vol. I, pp. 311. Academic Press, New York, London (1963).

² A.P.N. Franchimont and A. Lublin, *Rec. Trav. Chim.* **21**, 45 (1902).

³ M. Kohn, *Monatsh.* **26**, 939 (1905).

⁴ R. Delaby, R. Damiens and G. d'Huytèze, *Compt. rend.* **239**, 674 (1954).

⁵ H.K. Hall and A.K. Schneider, *J. Amer. Chem. Soc.* **80**, 6409 (1958).

⁶ E.K. Drechsel, *U. S. Pat.* 2,744,897 (1956); *Chem. Abstr.* **51**, 498 (1957).

⁷ H.K. Sen and Ch. Barat, *Quart. J. Indian Chem. Soc.* **3**, 405 (1926); *Chem. Abstr.* **21**, 3614 (1927).

⁸ A.M. Paquin, *Z. Naturforsch.* **1**, 518 (1946); *Chem. Abstr.* **42**, 123 (1948).

⁹ R.N. Lacey, *J. Chem. Soc.* 845 (1954).

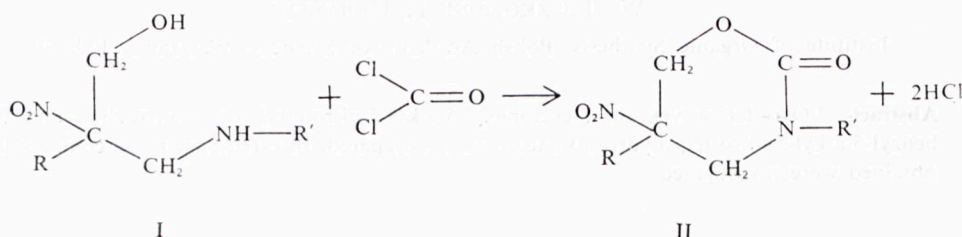
¹⁰ K. Gulbins, G. Benzing, R. Maysenhölder and K. Hamann, *Chem. Ber.* **93**, 1975 (1960).

¹¹ S.L. Shapiro, V. Bandurco and L. Freedman, *J. Org. Chem.* **26**, 3710 (1961).

¹² R.N. Lacey and W.R. Ward, *J. Chem. Soc.* 2134 (1958).

used, but in this case the synthesis was carried out in a few stages.¹³⁻¹⁵ Testa and co-workers¹⁶ prepared 5-phenyl-5-ethyl-tetrahydro-1,3-oxazin-2-one by the direct action of phosgene on the corresponding aminoalcohol.

The method of preparation of 5-alkyl-5-nitro-tetrahydro-1,3-oxazin-2-ones, chosen in our work, involved direct reaction of phosgene with corresponding amino-nitroalcohols in the presence of pyridine, which combined the hydrogen chloride evolved during the reaction.



Amino-nitroalcohols used in the reaction were prepared by the well-known methods, that is, condensation of nitrodiols with cyclohexylamine ($\text{R}'=\text{cyclohexyl}$)¹⁷ or ring opening of 3-benzyl-5-alkyl-5-nitro-tetrahydro-1,3-oxazines ($\text{R}'=\text{benzyl}$).¹⁸

The reaction was carried out in mild conditions in toluene/ether solution (the reaction proceeds well also in toluene solution) with stoichiometric amounts of the starting materials. 5-alkyl-5-nitro-tetrahydro-1,3-oxazin-2-ones, substituted by the cyclohexyl or benzyl group in position 3 were prepared in 33–46% yield.

The compounds obtained possess the characteristic grouping $\text{C}-\text{O}-\text{C}(=\text{O})-\text{N}-\text{C}$ which is a fragment of the six-membered ring; therefore, they can be regarded as intramolecular urethans.

The structure of these compounds was proved by infrared spectral analysis. The spectra possess neither 3600 nor 3500–3300 cm^{-1} bands, characteristic for the starting amino-nitroalcohols (Fig. 1).

The lack of these bands in the spectra of the reaction products indicates that the hydroxyl group and the secondary amino group of the starting amino-nitroalcohols disappeared during the reaction. Instead, the reaction products exhibit a new strong band near 1700 cm^{-1} . Since the compounds in question represent a very close analogy simultaneously to δ -lactams or δ -lactones, this band can be assigned to the carbonyl group vibrations which, in the case of δ -lactams

¹³ A.W. Dox and L. Yoder, *J. Amer. Chem. Soc.* **45**, 723 (1923).

¹⁴ S.R. Safir and R.J. Lopresti, *U.S. Pat.* 2,797,217 (1957). *Chem. Zentr.* 3908 (1959).

¹⁵ American Cyanamid Co., *Brit. Pat.* 773,011 (1957); *Chem. Zentr.* 219 (1959).

¹⁶ E. Testa, L. Fontanella and G.F. Cristiani, *Farmaco (Pavia, Ed. Sci.* **13**, 437 (1958); *Chem. Abstr.* **53**, 6099 (1959).

¹⁷ T. Urbański and D. Gürne, *Roczniki Chem.* **31**, 869 (1957).

¹⁸ D. Gürne and T. Urbański, *Roczniki Chem.* **31**, 855 (1957).

and δ -lactones appear according to Bellamy,¹⁹ in the range of 1680 and 1750–1735 cm^{-1} , respectively. It should be pointed out that the band is quite broad (about 10–15 cm^{-1}).

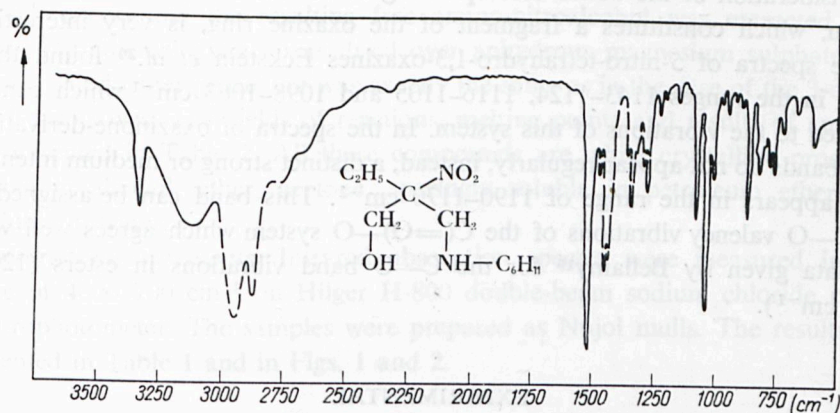


FIG. 1. The infrared spectrum of 2-nitro-2-ethyl-3-hydroxypropyl-N-cyclohexylamine. Dashed line Nujol bands.

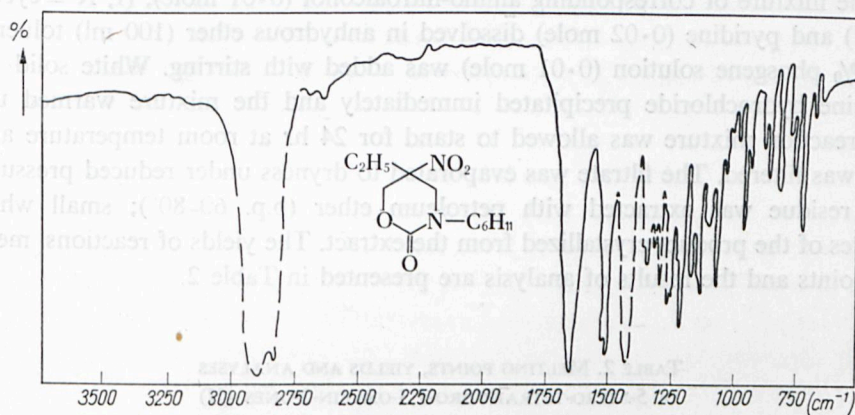


FIG. 2. The infrared spectrum of 5-nitro-5-ethyl-3-cyclohexyltetrahydro-1,3-oxazin-2-one. Dashed line Nujol bands.

TABLE 1. INFRARED ABSORPTION BANDS OF 5-NITRO-TETRAHYDRO-1,3-OXAZIN-2-ONES (II). FREQUENCIES IN cm^{-1}

R'	R	C=O	NO ₂	C—O
Cyclo-C ₆ H ₁₁	C ₂ H ₅	1689s	1547s	1170s
Cyclo-C ₆ H ₁₁	n-C ₃ H ₇	1712m; 1690s	1552s	1182m
C ₆ H ₅ CH ₂	CH ₃	1703s; 1691s	1559s	1589s
C ₆ H ₅ CH ₂	C ₂ H ₅	1710s; 1696s	1547s	1172s
C ₆ H ₅ CH ₂	n-C ₃ H ₇	1708s; 1689s	1542s	1177m

¹⁹ L. J. Bellamy, *The Infra-red Spectra of Complex Molecules*, Wiley and Sons, New York (1958).

Besides the 1700 cm^{-1} band, the spectra investigated exhibit a strong band at 1550 cm^{-1} . This band corresponds to the nitro group stretching vibrations.

Consideration of the bands corresponding to the vibrations of the C—O—C system, which constitutes a fragment of the oxazine ring, is very interesting. In the spectra of 5-nitro-tetrahydro-1,3-oxazines Eckstein *et al.*²⁰ found three bands in the ranges 1143–1124, 1116–1105 and $1098\text{--}1063\text{ cm}^{-1}$ which can be assigned to the vibrations of this system. In the spectra of oxazinone-derivatives these bands do not appear regularly, instead, a distinct strong or medium intensity band appears in the range of $1190\text{--}1170\text{ cm}^{-1}$. This band can be assigned to the C—O valency vibrations of the C(=O)—O system which agrees well with the data given by Bellamy¹⁹ for the C—O band vibrations in esters ($1200\text{--}1150\text{ cm}^{-1}$).

EXPERIMENTAL

Preparation of 3-cyclohexyl-5-alkyl-5-nitro-tetrahydro-1,3-oxazin-2-ones (II). To the mixture of corresponding amino-nitroalcohol (0.01 mole), (I, R' = cyclohexyl) and pyridine (0.02 mole) dissolved in anhydrous ether (100 ml) toluenic 12.5% phosgene solution (0.01 mole) was added with stirring. White solid of pyridine hydrochloride precipitated immediately and the mixture warmed up. The reaction mixture was allowed to stand for 24 hr at room temperature and then was filtered. The filtrate was evaporated to dryness under reduced pressure. The residue was extracted with petroleum ether (b.p. $60\text{--}80^\circ$); small white needles of the product crystallized from the extract. The yields of reactions, melting points and the results of analysis are presented in Table 2.

TABLE 2. MELTING POINTS, YIELDS AND ANALYSES
OF 5-NITRO-TETRAHYDRO-1,3-OXAZIN-2-ONES (II)

R'	R	M.p., °C	Yield, %	Analysis, %						
				Found			Formula	Requires		
				C	H	N		C	H	N
Cyclo-C ₆ H ₁₁	C ₂ H ₅ ^a	103–104	46	56.3	7.8	10.8	C ₁₂ H ₂₀ O ₄ N ₂	56.2	7.9	10.9
Cyclo-C ₆ H ₁₁	n-C ₃ H ₇	86–87	40	57.8	8.4	10.5	C ₁₃ H ₂₂ O ₄ N ₂	57.8	8.2	10.4
C ₆ H ₅ CH ₂	CH ₃	109–111	40	57.3	5.4	11.3	C ₁₁ H ₁₄ O ₄ N ₂	57.6	5.6	11.2
C ₆ H ₅ CH ₂	C ₂ H ₅	96–97	46	59.1	6.5	10.6	C ₁₂ H ₁₆ O ₄ N ₂	59.1	6.1	10.6
C ₆ H ₅ CH ₂	n-C ₃ H ₇	100–102	33	60.7	6.4	10.3	C ₁₃ H ₁₈ O ₄ N ₂	60.4	6.5	10.1

^a Molecular weight of 3-cyclohexyl-5-ethyl-5-nitro-tetrahydro-1,3-oxazin-2-one was determined by the cryoscopic method in dioxane. (Found: 268. C₁₂H₂₀O₄N₂ requires: 256.3).

²⁰ Z. Eckstein, P. Gluziński, W. Hofman and T. Urbański, *J. Chem. Soc.* 489 (1961).

Preparation of 3-benzyl-5-alkyl-5-nitro-tetrahydro-1,3-oxazines-2-ones (II). To the corresponding amino-nitroalcohol (I, $R' = \text{benzyl}$) hydrochloride (0.01 mole), dissolved in small amount of water aqueous sodium bicarbonate was added in a small excess and the resulting free amino-nitroalcohol was extracted with ether. The ethereal extract was dried over anhydrous magnesium sulphate and filtered. The further procedure was exactly the same as in the case of the 3-cyclohexyl derivatives. The yields of reactions, melting points and results of analysis are presented in Table 2. All these compounds are white crystalline products, soluble in alcohol, ether, acetone, sparingly soluble in petroleum ether and insoluble in water.

Infrared measurements. Infrared absorption spectra were measured in the range of $4000\text{--}700\text{ cm}^{-1}$ on Hilger H-800 double-beam sodium chloride prism spectrophotometer. The samples were prepared as Nujol mulls. The results are presented in Table 1 and in Figs. 1 and 2.

